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(21) International Application Number: PCT/EP99/04874 (22) International Filing Date: 12 July 1999 (12.07.99) (30) Priority Data: MI98A001774 30 July 1998 (30.07.98) IT (71) Applicant: ZAMBON GROUP S.P.A. [IT/IT]; Via della Chimica, 9, I-36100 Vicenza (IT). (72) Inventors: GRASSANO, Alessandro; Via Voltorno, 21, I-20052 Monza (IT). MARCHIORRI, Maurizio; Via Don Orsenigo, 11, I-22039 Valbrona (IT). DI TORO, Mauro; Via Vittorino Mandelli, 18/A, I-20050 Ronco Briantino (IT). CASTEGINI, Franco; Strada Gogna, 37, I-36100 Vicenza (IT). (74) Agent: LONGONI, Alessandra; Zambon Group S.p.A., Corp. Patent & Trademark Dept., Via Lillo del Duca, 10, I-20091 Bresso (IT).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: FAST DISSOLVING IBUPROFEN CONTAINING COMPOSITIONS HAVING ANALGESIC ACTIVITY		
(57) Abstract An analgesic composition useful in the preparation of fast dissolving tablets is provided wherein the composition is the result of combining ibuprofen, arginine, linear PVP and an alkaline bicarbonate to which usual excipients for the preparation of tablet are added.		

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FAST DISSOLVING IBUPROFEN CONTAINING COMPOSITIONS HAVING ANALGESIC ACTIVITY

The present invention relates to an analgesic composition for preparing fast dissolving tablets containing ibuprofen and arginine and the tablets made therefrom.

Ibuprofen is the International common name of the compound 2-(4-isobutylphenyl)-propionic acid, which is a known drug with analgesic, as well as anti-inflammatory and antipyretic, activity of broad diffusion.

In U.S. Patent No. 4,279,926 (SPA-Società Prodotti Antibiotici S.p.A.) ibuprofen salts with basic amino acids such as arginine and lysine have been described. To our knowledge only the lysine salt has been commercialised.

In U.S. Patent No. 4,689,218 (Zambon Group S.p.A.) effervescent compositions of ibuprofen containing arginine together with 20-30% by weight of bicarbonate and 25-40% by weight of sodium bitartrate have been described.

The described formulations are useful for preparing drinkable aqueous solutions.

In U.S. Patent No. 4,834,966 (Zambon Group S.p.A.) non-effervescent compositions are disclosed consisting, as a base, of a ternary mixture consisting of ibuprofen, 1.1 to 1.5 mol% arginine per mole of ibuprofen and sodium bicarbonate in a weight amount between 0.25 and 0.75 times the weight of ibuprofen.

These formulations are disclosed as very suitable for the preparation of granulates quickly soluble in water.

The administration of the so obtained aqueous solutions assures a fast analgesic effect which is achieved in about ten minutes.

Sachets containing the granulate of US 4,834,966 are on the market.

In some Countries, and in particular in the U.S.A., the preparations in the form of a sachet are not particularly appreciated by the public, who generally prefer the use of tablets in the treatment of conditions which need an analgesic drug.

The commercially available tablets containing ibuprofen do not have a particularly fast effect because they require about 30 minutes to completely dissolve and reach the blood stream.

In order to obtain a quick dissolution of the active principle, the present inventors tried preparing tablets starting from the ibuprofen-arginine-sodium bicarbonate ternary mixture of

- 2 -

the above mentioned U.S. Patent No. 4,834,966.

Unfortunately, it was impossible to obtain satisfactory results because the resulting tablets were too friable and subject to fragmentation during manufacturing and packaging.

5 Therefore, there was the problem to have available tablets having good workability and a fast dissolution so as to assure a prompt analgesic effect.

These results have been obtained thanks to a new mixture containing ibuprofen, arginine, linear polyvinylpyrrolidone (PVP) and a reduced amount of an alkaline bicarbonate.

Therefore, an object of the present invention is an analgesic composition comprising
10 ibuprofen; from 1.1 to 1.5 moles of arginine per mole of ibuprofen; from 0.5 to 10% by weight of linear PVP with respect to the weight of ibuprofen; and from 5 to 10% by weight of an alkaline bicarbonate respect to the weight of ibuprofen.

A further object of the present invention is a fast dissolution tablet comprising ibuprofen; from 1.1 to 1.5 moles of arginine per mole of ibuprofen; from 0.5 to 10% by weight of linear
15 PVP with respect to the weight of ibuprofen; and from 5 to 10% by weight of an alkaline bicarbonate respect to the weight of ibuprofen and including also normal excipients useful for the preparation of tablets.

Preferably ibuprofen is contained in amounts of from 100 to 400 mg/tablet, more preferably in amounts of 100, 200 mg/tablet, most preferably in an amount of 200 mg/tablet.

20 Arginine is preferably contained in an amount from 1.1 to 1.3 moles per mole of ibuprofen and more preferably in an amount of 1.2 moles per mole of ibuprofen.

Linear PVP is preferably a PVP having an average K value, determined according to the method described in the U.S. Pharmacopoeia XXIII, of from 25 to 90, more preferably from 50 to 90, most preferably PVP K90. It is preferably used in an amount of from 2 to 8% by
25 weight with respect to the weight of ibuprofen.

The alkaline bicarbonate is sodium and potassium bicarbonate and it is preferably used in an amount of from 7 to 10% by weight with respect to the weight of ibuprofen.

Within the present context the identity of the components and amounts thereof refer to the weight and identity of the starting materials used in preparing the composition. It is possible
30 that during preparation of the composition and/or tablets, some interaction or reaction may

- 3 -

occur between two or more components. To the extent that such interaction or reaction occurs the present invention is intended to cover such occurrences.

Normal excipients useful in the preparation of the tablets include, but are not limited to:

5 lubricants such as magnesium stearate, sodium stearyl fumarate and sodium benzoate; anti-adherents such as talc and polyethylenglycol; glidants such as colloidal silica; diluents such as dicalcium phosphate, cellulose (for example microcrystalline cellulose) and its derivative, carbohydrates and polyalcohols such as saccharose, xylitol and lactose; disintegrants such as reticulate vinylic polymers (such as crosslinked PVP), derivatives of starch and of cellulose

10 such as sodium carboxymethyl-starch and sodium croscarmellose; wetting agents such as TWEEN 80 (Trademark registered by ICI of Americas for polysorbate) and sodium lauryl sulphate.

Suitable excipients and their amounts can be readily determined by the man skilled in the art according to the methods normally used in pharmaceutical technology. However, in the

15 present invention, it is important to avoid excipients that would cause a significant decrease in tablet dissolution rate. Further, excipients must allow a good workability of the tablet.

In preparing the tablet of the present invention it is preferable to prepare a granulate with the mixture of ibuprofen, arginine and linear PVP, to mix to it the bicarbonate and the excipients, and then to compress.

20 When desired, the tablets can be film coated with a coating readily soluble in the gastric environment.

Suitable coatings can be prepared using conventional tablet coating compositions and methods. Preferred coatings include OPADRY II (sold by Colorcon; a mixture of hydroxypropyl methyl cellulose, pigments and a plasticizer), EUDRAGIT (sold by Rohm

25 Pharma; a methacrylic acid ester polymer) and a combination of OPADRY II with saccharose.

The granulate can be prepared by direct granulation of the three components (ibuprofen, arginine and liner PVP) in the desired amounts or, after a first granulation of arginine with melted ibuprofen, by granulating a second time with linear PVP.

30 Both granulates obtained according the above described methods are then screened, dried,

- 4 -

combined with bicarbonate and any selected excipient(s) in the desired amounts and compressed in suitable moulds for obtaining the desired tablets which can then be film coated, if desired.

- 5 In addition to good handling and good workability, the tablets of the present invention provide complete dissolution of the active ingredient in about 10 minutes or less. Consequently the release is faster with respect to the commercially available ibuprofen based analgesic tablets (see example 5).

Generally, linear PVP is considered a binder at the amounts used in the present invention,
10 and would be thus expected to inhibit dissolution or have little or no effect on dissolution. With the aim to better illustrate the present invention the following examples are now given.

Example 1

Method for the preparation of the granulate of ibuprofen, arginine and linear PVP

Into an Erweka planetary mixer equipped with a thermostatic jacket bowl the entire quantity
15 of ibuprofen was charged and melted at a temperature of 80°C under continuous stirring. After all ibuprofen was entered, arginine, PVP and boiling water were added in that order. After about 10 minutes of continuous stirring a creamy mass was obtained which was slowly cooled down to room temperature thus obtaining a solid granular mass.

Drying was completed by placing the granulate in a whirlpool static oven regulated at a
20 temperature of 45°C for about 15 hours.

An alternative procedure involved preparing the ibuprofen and arginine granulate, to which powdered linear PVP was added and a second granulation of the mixture with cold water was carried out. The wet granulate obtained was dried in a whirlpool static oven. The alkaline bicarbonate and the excipients were then added.

25

Example 2

Alternative method for the preparation of ibuprofen, arginine and linear PVP granulate

Into a fast granulator water and arginine were sequentially introduced. When the arginine was partially dissolved, ibuprofen and linear PVP were added in sequence, and the mixture warmed under continuous stirring for about 30 minutes to obtain a creamy mass.

30 The creamy mass was then dried under vacuum for about 50 minutes.

- 5 -

At the end of drying the obtained mass was screened through an oscillating granulator equipped with a 1.5 mm sieve.

To the obtained granulate, bicarbonate and the excipients were then added.

- 5 The above described granulation method was also used in the preparation of an ibuprofen-arginine granulate to which powdered linear PVP was subsequently added.

The resulting mixture was granulated with cold water and the wet granulated product was dried in a static oven or directly into the granulator. The bicarbonate and the excipients were then added.

10

Example 3

Preparation of tablets

The granulate containing ibuprofen-arginine and linear PVP, obtained according to the procedure described in the example 1 or in the example 2, and to which bicarbonate and the excipients were added, was compressed to the desired weight.

15

Example 4

By operating according to the procedure described in the example 3, the tablets whose composition is reported in the following table 1 were prepared.

- 6 -

Table 1

Compositions according to the invention

Ingredients	Tablets (mg)						
	A	B	C	D	E	F	G
Ibuprofen	200	200	200	200	200	400	400
Arginine	185	185	185	185	185	370	370
PVP K90	5.4	5.4	5.4	5.4	5.4	10.8	10.8
Sodium bicarbonate	20	20	20	15	20	40	40
Microcrystalline cellulose	156			156	141	103	
Lactose		156					103
Dicalcium phosphate			156				
Sodium croscarmellose				30			
Sodium carboxymethyl starch			30				50
Reticulate PVP	30	30			30	50	
Magnesium stearate	3.0	3.0	3.0	3.0	3.0	5.0	5.0
Colloidal silica	0.6	0.6	0.6	0.6	0.6	1.2	1.2
Tablet total weight (mg)	600	600	600	600	600	980	980

5

Example 5**Determination of the dissolution rate of tablets of the present invention**

Determination of the dissolution rate was carried out by applying the method described in the U.S. Pharmacopeia XXIII, NF XVII, supplement No. 5.

10 Into a dissolution bath a solution of pH 7.2 phosphate buffer was charged and the liquid was thermostated at a temperature of 37°C.

The tablet to be checked was then charged and under continuous stirring by paddle at 50 rpm, the amount of ibuprofen in solution, expressed in percentage released as a function of time, was measured.

15 The tablets of the invention had an excellent dissolution rate in comparison with commercially available tablets containing the same amount of ibuprofen.

- 7 -

As an example, the ibuprofen contained in tablet A (see table I) was completely in solution in 10 minutes according to the above described test, while a tablet of MOTRIN® (Upjohn) and one of ANTALGIL® (Jannsen-Cilag), containing the same amount of ibuprofen of
5 tablet A, showed the release of a percentage of ibuprofen in solution of about 45% and 65% respectively, after 10 minutes.

It was necessary to wait at least 30 minutes before observing complete dissolution of the ibuprofen contained in the MOTRIN® and ANTALGIN® tablets.

- 8 -

Claims

- 1) An analgesic composition comprising ibuprofen; from 1.1 to 1.5 moles of arginine per mole of ibuprofen; from 0.5 to 10% by weight of linear PVP with respect to the weight of
5 ibuprofen; and from 5 to 10% by weight of an alkaline bicarbonate respect to the weight of ibuprofen.
- 2) A fast dissolving tablet comprising ibuprofen; from 1.1 to 1.5 moles of arginine per mole of ibuprofen; from 0.5 to 10% by weight of linear PVP with respect to the weight of ibuprofen; and from 5 to 10% by weight of an alkaline bicarbonate respect to the weight of
10 ibuprofen and including also normal excipients useful for the preparation of tablets.
- 3) A tablet according to claim 2, wherein the ibuprofen is present in an amount of from 100 to 400 mg.
- 4) A tablet according to claim 2, wherein the ibuprofen is present in an amount of from 200 to 400 mg.
- 15 5) A tablet according to claim 2, wherein arginine is present in an amount of from 1.1 to 1.3 moles per mole of ibuprofen.
- 6) A tablet according to claim 5, wherein the arginine:ibuprofen molar ratio is 1.2:1.
- 7) A tablet according to claim 2, wherein the linear PVP has an average K value of from 25 to 90.
- 20 8) A tablet according to claim 7, wherein the linear PVP is PVP K90.
- 9) A tablet according to claim 2, wherein the alkaline bicarbonate is sodium or potassium bicarbonate.
- 10) A tablet according to claim 2, wherein ibuprofen is present in an amount of 200 or 400 mg, arginine is present in an amount of 1.2 moles per mole of ibuprofen, the linear PVP
25 is PVP K90 and the alkaline bicarbonate is sodium bicarbonate.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

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According to International Patent Classification (IPC) or to both national classification and IPC

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IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 93 09763 A (ISP INVESTMENTS INC.) 27 May 1993 (1993-05-27) page 1 claims 1-5	1-10
Y	GB 2 279 250 A (ZAMBON S.P.A.) 4 January 1995 (1995-01-04) examples 9,10	1-10
A	WO 97 30699 A (THE BOOTS COMPANY PLC) 28 August 1997 (1997-08-28) claims 1-15 examples 24-26	1-10
A	DE 36 38 414 A (ZAMBON S.P.A.) 21 May 1987 (1987-05-21) & US 4 689 218 A cited in the application	1-10

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A	FR 2 602 141 A (ZAMBON SPA) 5 February 1988 (1988-02-05) & US 4 834 966 A cited in the application -----	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/04874

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9309763	A	27-05-1993	US 5262171 A	16-11-1993
			AU 3136293 A	15-06-1993
GB 2279250	A	04-01-1995	IT 1264856 B	17-10-1996
			BE 1007194 A	18-04-1995
			CA 2125643 A	22-12-1994
			CH 687850 A	14-03-1997
			DE 4420856 A	22-12-1994
			DK 72594 A	22-12-1994
			ES 2099021 A	01-05-1997
			FR 2706892 A	30-12-1994
			HU 9500467 A	28-09-1995
			JP 7101855 A	18-04-1995
			NL 9401005 A	16-01-1995
			NO 942343 A	22-12-1994
			SE 9402157 A	22-12-1994
			US 5500226 A	19-03-1996
			US 5645857 A	08-07-1997
WO 9730699	A	28-08-1997	AU 1793797 A	10-09-1997
			BG 102744 A	31-05-1999
			CA 2246344 A	28-08-1997
			CN 1215989 A	05-05-1999
			CZ 9802617 A	11-11-1998
			EP 0881899 A	09-12-1998
			HU 9901454 A	30-08-1999
			NO 983825 A	20-10-1998
			PL 328465 A	01-02-1999
			SK 114298 A	11-01-1999
DE 3638414	A	21-05-1987	IT 1209667 B	30-08-1989
			AT 395372 B	10-12-1992
			AU 6509886 A	14-05-1987
			BE 905737 A	12-05-1987
			CA 1276113 A	13-11-1990
			CH 674934 A	15-08-1990
			FR 2590893 A	05-06-1987
			GB 2189994 A, B	11-11-1987
			GR 862697 A	10-03-1987
			IE 59055 B	15-12-1993
			JP 7061941 B	05-07-1995
			JP 62149615 A	03-07-1987
			MX 9203170 A	01-07-1992
			NL 8602870 A, B,	01-06-1987
			US 4689218 A	25-08-1987
FR 2602141	A	05-02-1988	IT 1197038 B	25-11-1988
			AT 394945 B	27-07-1992
			AU 595342 B	29-03-1990
			AU 7554087 A	04-02-1988
			BE 1002109 A	10-07-1990
			BG 60832 B	30-04-1996
			CA 1286992 A	30-07-1991
			CH 673394 A	15-03-1990
			DE 3725176 A	04-02-1988
			GB 2193093 A, B	03-02-1988
			GR 871197 A	04-12-1987
			IE 60276 B	29-06-1994

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/04874

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR 2602141 A		JP 2585005 B	26-02-1997
		JP 63041420 A	22-02-1988
		MX 9203167 A	01-07-1992
		NL 8701729 A	01-03-1988
		US 4834966 A	30-05-1989
		ZA 8705397 A	01-02-1988
